Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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ONLINE SUPPLEMENT

Continuous Positive Airway Pressure, Weight Loss, or Both for Obstructive Sleep Apnea

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Supplemental Methods

Inclusion and exclusion criteria

Inclusion and exclusion criteria are shown in online Table 1.

In-Lab Diagnostic polysomnography

The 12-channel confirmatory diagnostic polysomnogram recorded electro-encephalograms, eye, chin and pre-tibial muscle activity, electrocardiography, oximetry, chest and abdominal respiratory effort, and airflow by nasal cannula and oral thermistor [Sandman System (Embla® Systems Inc, Broomfield, CO)]. Trained technicians scored the polysomnographic recordings and computed the apnea-hypopnea index (AHI) as (apneas+hypopneas)/hours of sleep time. An apnea was defined as ≥10 seconds of airflow cessation. A hypopnea required ≥10 seconds of reduction in airflow: 1) either ≥50%, or 2) ≥30% with >3% fall in SaO2 or an arousal.

Oxyhemoglobin saturation data were reviewed and artifact was excluded by a trained PSG technologist. Using the remaining (valid) oxyhemoglobin saturation data values during sleep, we computed the average value and also selected the nadir SaO2 during sleep. We also computed percent time below 90% (%time<90%) as minutes with saturation value < 90% divided by total sleep time. The oxygen desaturation index-4 (ODI4) was calculated as the hourly rate of desaturations of at least 4% magnitude, compared against the immediately preceding baseline, during sleep. The oxygen desaturation index-3 (ODI3) was calculated as the hourly rate of desaturations of at least 3% magnitude, compared against the immediately preceding baseline, during sleep. Arousals were scored using criteria defined by the American Sleep Disorders Association.[1] The arousal index was computed as the number of arousals divided by sleep time in hours.

The Epworth Sleepiness Scale was used to measure the level of subjective sleepiness.[2] This 8-item scale sums subjects' self-rated chance of dozing, on a scale of 0-3, during eight sedentary situations. Scores range from 0-24, and a score >10 is considered abnormal. Subjects rate their chance of dozing in each situation as none (0), slight (1), moderate (2) or high (3). The sedentary situations are: watching television, reading, sitting inactive in a public place, lying down to rest in the afternoon when circumstances permit, sitting quietly after lunch without alcohol, in a car as a passenger for an hour without break, during conversations, and while driving and stopped in traffic.

Assessment of insulin sensitivity

The frequently sampled intravenous glucose tolerance test (FSIGTT) was used to assess insulin sensitivity. This test is performed after a 12-hour overnight fast, and involves blood sampling at baseline (time = -15, -10, and -5 min) and at time = 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 30, 40, 50, 70, 100, 140, & 180 min post-injection of glucose (0.3 g/kg over 1 min starting at t = 0) with an injection of insulin (0.03 U/kg over 30 seconds) occurring at t = 20 min. Each sample is assayed for glucose and insulin, allowing for the calculation of the insulin sensitivity index using Bergman's minimal model,[3] using MinMod Millenium® software.[4]

Bioassays and blood pressure measurements

C-reactive protein levels and various lipid parameters were measured in blood samples drawn after an overnight fast and immediately centrifuged, with the serum kept at –70^{o}C for batch analyses. C-reactive protein was measured with an ultra-high sensitivity latex

turbidometric immunoassay (Wako Pure Chemical Industries, Ltd, Osaka Japan) on a Cobas Fara II Analyzer. Serum high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides were measured on a Cobas Fara II high-speed autoanalyzer (Roche Diagnostic Systems, Inc.). Serum lipoprotein subfractions were measured by nuclear magnetic resonance spectroscopy (LipoScience, Inc) as previously described.[5]

Insulin was measured by radioimmunoassay (Laboratory Corporation of America) and glucose by enzymatic calorimetric assay (Wako Diagnostics).

Blood pressure measurements were performed with the oscillometric method in the fasting state, between 8:00 and 9:00 AM, before any blood draws and the initiation of the frequently-sampled intravenous glucose tolerance test.

Rationale for inclusion of adherent subjects in the primary per-protocol analyses

We hypothesized that OSA is a primary cause of inflammation, insulin resistance and that CPAP therapy would therefore improve these quantitative endpoints and that combined therapy will improve it more than either therapy alone. The effectiveness of weight loss in producing improvements in these endpoints was hypothesized to arise from both a direct effect of reductions in body weight and an indirect effect, which results from a reduction in sleep apnea severity. Our experimental design allows for estimations of the magnitude of the incremental effects of weight loss and CPAP through estimation of linear contrasts. Assuming that weight loss therapy actually reduces body weight and that CPAP therapy

actually treats OSA effectively, for a given quantitative endpoint (E), the assessment would be as follows:

(1) Incremental benefit of Weight Reduction = μΔE (Combination therapy arm) - μΔE (CPAP arm)

(2) Incremental benefit of OSA reduction = μΔE (Combination therapy arm) - μΔE (Weight loss arm)

Where μΔE (tx) is the observed change in the endpoint (E) achieved by treatment 'tx'.

If any incremental benefit is observed in subjects undergoing weight loss relative to a group that receives effective treatment for OSA, it follows that the effect can only be attributed to direct effects of obesity that are independent of OSA. Similarly, incremental effects observed in subjects undergoing effective CPAP therapy relative to a group that experiences only weight reduction, it follows that the effect can be attributed to direct effects of OSA that are independent of obesity even if some improvement in OSA occurs as a result of weight loss.

It is important to note that for the rationale explained above to be valid, estimation of these contrasts (and thus the incremental benefit of CPAP and weight loss) require an actual reduction in weight loss and an actual treatment that effectively reduces OSA. Thus, our primary per-protocol analyses that aimed at assessing the causal effects of OSA vs. obesity, pre-specified the inclusion of only subjects who met pre-defined adherence criteria to weight loss therapy (≥5% reduction in body weight) and CPAP therapy (average CPAP use of ≥4 hours per night on ≥70% of the nights). However, given the importance of intention-

to-treat effects from a clinical standpoint, we also present intent-to-treat analyses, which assessed the relative average efficacy of our interventions in the entire randomized sample.

Interpretation of changes in the natural logarithm of CRP

The distribution of hsCRP variable in the study population was found to be skewed. Therefore, a natural logarithmic (ln) transformation was applied for inferential modeling. In such models, the outcome is the change in ln-CRP from baseline:

$$\ln(v2) - \ln(v1)$$

where $v2$ is the value of CRP after the intervention and $v1$ is the value of CRP at baseline. Such difference in natural log-transformed values is not easily interpretable. We therefore chose to express this estimate after further transformation, in order to obtain values that reflect a percent change of the "raw" (untransformed) CRP value relative to baseline:

$$\text{Percent change in CRP} = \ 100 * (e^{\ln(v2) - \ln(v1)} - 1)$$

The mathematical proof of this relationship is presented below. Because the difference between 2 logarithms equals the logarithm of their ratio, it follows that:

$$100 * (e^{\ln(v2) - \ln(v1)} - 1) = \ 100 * (e^{\ln(\frac{v2}{v1})} - 1)$$

Because e and ln cancel each other out:

$$100 * (e^{\ln(\frac{v2}{v1})} - 1) \ = 100 * (\frac{v2}{v1} - 1)$$

Since 1=$v1/v1$ and because of a common denominator:

$$100 * (\frac{v2}{v1} - 1) = \ 100 * (\frac{v2}{v1} - \frac{v1}{v1}) = 100 * (\frac{v2 - v1}{v1}) = \text{Percent change in CRP}$$

Role of Investigators

Frederick F. Samaha, A.I.P, I.G., G.M., G.F., K.T. and D.J.R. designed the study; the data was gathered by J.A.C., A.I.P., I.G., P.B., H.S., R.R.T. and T.W; K.T. performed modeling of insulin sensitivity using frequently sampled intravenous tolerance test data. A.L.H and J.C. analyzed the data; J.A.C., A.L.H and J.C. vouch for the data and analysis; J.A.C. wrote the first draft of the manuscript; all authors approved the final version. The authors had full access to data and full control of the decision to publish.

Supplemental Results

Online Table 2 shows baseline characteristics of subjects randomized to each study arm, meeting pre-specified adherence criteria. Online Figure S1 shows the changes in changes in body weight (A), LDL-cholesterol (B), HDL-cholesterol (C), LDL-particle concentracion(D) and HDL-particle concentration (E) compared to baseline in intention-to-treat analyses (left panels) and per-protocol analyses including only subjects who met pre-specified adherence criteria (right panels). Online Figure S2 shows the changes in ,ean arterial pressure (A) pulse pressure (B) compared to baseline in intention-to-treat analyses (left panels) and per-protocol analyses including only subjects who met pre-specified adherence criteria (right panels). Online Table 3 shows the change in body weight and various study endpoints from baseline, at 8 weeks and 24 weeks, as shown in Figures 2-3 and online figures S1-S2. Online Table 4 shows adverse events reported during the trial.

Sensitivity analyses using the baseline value-carried forward approach

We performed sensitivity analyses in which the baseline value was carried forward for subjects who dropped out of the study and therefore did not have available data at 8 and 24 weeks. The results of these analyses are shown in online Table 4. Although the estimated within-group changes in the study endpoints were of lower magnitude in these analyses, results from between-group comparisons yielded trends that were similar to those observed in the primary modified intention-to-treat analyses.

These sensitivity analyses did not include LDL- and HDL-particle concentrations, since nuclear magnetic resonance spectroscopy was performed only in stored biosamples from subjects who had at least one follow-up measure after randomization.

Changes in medication use during the trial

Changes in antihypertensive, lipid-lowering and other medications were left at the discretion of the subjects' healthcare providers.

Anti-hypertensive medications: Overall, 12 subjects experienced a change in the antihypertensive medication regimen after the baseline visit. Of these, 8 met compliance criteria for inclusion in sub-group per-protocol analyses. In the weight loss only arm, 2 subjects experienced initiation of a new antihypertensive medication or a dose increase, whereas 3 subjects experienced a dose reduction or discontinuation. In the CPAP-only arm, 1 subject experienced initiation of a new antihypertensive medication or a dose increase, whereas 4 subjects experienced a dose reduction or discontinuation. In the combination-therapy arm, 1 subject experienced initiation of a new antihypertensive medication or a dose

increase, whereas 1 subject experienced a dose reduction or discontinuation. Sensitivity analyses assessing the change in blood pressure among subjects who did not experience a change in the antihypertensive medication regimen after the baseline are shown in online Table 6.

Lipid-lowering medications: Overall, 2 subjects experienced a change in lipid-lowering medications during the trial. One subject randomized to the CPAP-only arm experienced a dose increase, whereas one subject randomized to the weight loss-only arm experienced a dose reduction in a statin. None of these subjects met compliance criteria for inclusion in per-protocol subgroup analyses. No changes in other lipid-lowering medications occurred during the trial.

Glucose-lowering medications: No changes in glucose-lowering medications occurred during the trial.

Table S1. Inclusion and Exclusion Criteria

Inclusion Criteria

1. Age 18 to 80
2. Moderate to severe OSA (AHI ≥ 15 events/hour)
3. Body mass index of ≥ 30 kg/m
4. Baseline CRP > 1.0 mg/dl
5. Subject is capable of giving informed consent.

Exclusion Criteria

1. Predominant central sleep apnea
2. Type 1 Diabetes
3. Type 2 Diabetes associated with either: (a) unstable anti-diabetic therapy (anti-diabetic medication changes within past 3 months); (b) Hemoglobin A1C levels > 7%; (c) Inability to perform home blood glucose monitoring (fingerstick checks).
4. Required use of supplemental oxygen
5. Acute coronary syndrome or stroke within 3 months prior to study
6. A high-risk occupation or motor vehicle driving record, as defined by a score of 10 points or higher on an Occupational and Driving Habits Questionnaire.
7. Blood pressure >160/95 mmHg (may be re-screened after blood pressure control obtained)
8. Active infection, malignancy or chronic inflammatory disorders, or systemic steroid use
9. Unstable dose of statin therapy. Individuals taking statins will need to have been on a stable dose for at least 8 weeks prior to enrolling in the study.
10. Concomitant use of peroxisome proliferator-activated receptor (PPAR)-a (e.g. gemfibrozil and fenofibrate) or PPAR-g (e.g. rosiglitazone and pioglitazone).[6-9]
11. More than moderate alcohol use of > 14 drinks per week
12. Surgery within the previous 3 months (subjects may be enrolled after this 3-month period).
13. Sustained ventricular or supraventricular tachycardia ≥ 30 seconds during diagnostic sleep study
14. Known left ventricular ejection fraction < 30% or decompensated congestive heart failure requiring hospitalization within the past year.
15. Any episode of decompensated respiratory function requiring hospitalization within the past year
16. Evidence of severe restless leg syndrome or chronic pain syndrome that gives rise to frequent awakenings at night, noted during the sleep study. Such patients may still be enrolled if these other sleep disrupting disorders can be resolved prior to enrollment.
17. Female patients who are pregnant or likely to become pregnant (i.e. pre-menopausal and not using a form of birth control).
18. Severe depression, as defined by a Beck Depression Index of 29 or higher, or suicidal ideation.
19. Serious medical or psychological conditions that, in the opinion of the investigator, would compromise the subject's safety or successful participation in the study.
20. Diagnosis of erythrocytosis (Hemoglobin >18 for men and >16 for women).

Table S2. Baseline Characteristics of subjects randomized to each study arm, meeting pre-specified adherence criteria.

	Weight Loss (n=27)	CPAP (n=39)	CPAP + Weight Loss (n=24)	*P* value
Age, years	50.9 (11.8)	51.8 (9.3)	50.8 (11.4)	0.90
Male sex	13 (48.1%)	24 (61.5%)	13 (54.2%)	0.59
Race				
White	19 (76%)	24 (63.2%)	21 (87.5%)	0.10
Black	6 (24%)	14 (36.8%)	3 (12.5%)	
Mixed race or other	2 (7.4`%)	1 (2.56%)	0 (0%)	
Height, cm	171 (9.7)	173.6 (9.2)	172.6 (8.8)	0. 53
Weight, kg	112.3 (21.2)	114.7 (21.5)	112.5 (18.7)	0.87
Body Mass Index, kg/m^2	38.3 (5.5)	38.2 (7.2)	37.7 (5.5)	0.95
Total cholesterol, mg/dl	186.1 (42.3)	202.5 (35.8)	196.3 (37.8)	0.24
HDL-cholesterol, mg/dl	46.9 (11.6)	44.3 (9.3)	42.6 (11.1)	0.34
Triglycerides, mg/dl	121.9 (48.7)	140.6 (64)	160.2 (71)	0.09
LDL-cholesterol, mg/dl	115.9 (32.9)	128 (26.7)	116.4 (30)	0.17
Hypertension	11 (40.74%)	20 (54.05%)	5 (22.73%)	0.0630
Insulin Sensitivity Index, $\times 10^{-4}/min^{-1}$ /μU/mL)	1.4 (0.9)	1.2 (1.2)	1.7 (1.4)	0.43
Apoprotein A1, mg/dL	137.9 (21.1)	130.6 (15.2)	126.1 (22.3)	0.11
Apoprotein B, mg/dL	89.4 (24.8)	98.4 (22.8)	94.5 (20.5)	0.32
LDL particle size, nm	20.6 (0.7)	20.5 (0.8)	20.5 (0.6)	0.77
HDL particle size, nm	8.7 (0.3)	8.8 (0.4)	8.7 (0.3)	0.89
High-sensitivity CRP, mg/L	5.1 (1.7-8.5)	4.4 (2.3-8.2)	3.4 (2.0-7.0)	0.59
Systolic Blood Pressure, mmHg	125.8 (9.8)	129.7 (11.3)	123.8 (10.8)	0.10
Diastolic Blood Pressure, mmHg	77.6 (7.7)	80.8 (7.8)	75.7 (6.6)	0.034
Apnea-Hypopnea Index (events/hour)	38.3 (17.5)	44.7 (22.6)	45.6 (25.5)	0.42
Oxygen desaturation Index (>3% desaturation events/hour) *	21.2 (14.6)	28.5 (23.4)	27.3 (27.3)	0.42

Oxygen desaturation Index (>4% desaturation events/hour) *	16.4 (14)	22.9 (21.5)	22.6 (25)	0.42
Percent sleep time with SO_2 <90%	5.6 (9.1)	8.1 (15.2)	9.3 (18.4)	0.67
SO_2 Nadir During Sleep	76.6 (18.3)	75.7 (11.9)	77.7 (9.4)	0.86
Mean SO_2 During Sleep	94.4 (1.8)	94.5 (2.4)	93.9 (2.1)	0.53
Arousal Index *	33.5 (14.7)	40.5 (22.3)	42.7 (23.4)	0.26
Epworth Sleepiness Scale *	8.77 (3.68)	9.72 (4.37)	9.38 (4.22)	0.67
Current or Past Smoking	7 (25.9%)	11 (28.2%)	1 (4.2%)	0.06
Statin Use	7 (25.9%)	8 (20.5%)	4 (16.7)	0.72
Antihypertensive Medication Use	11 (40.7%)	18 (46.2%)	5 (20.8%)	0.12

SO_2= oxygen saturation. * For definitions, please refer to online appendix.

For High-sensitivity CRP, numbers indicate the median (interquartile range). Otherwise, numbers indicate the mean±standard deviation or counts (percentages).

Table S3. Change in Body Weight and Study Endpoints from baseline, at 8 weeks and 24 weeks, as shown in figures 2, 3, S1 and S2

		CPAP	WL+CPAP	WL	*Between-group P value, Week 24*		
					WL+CPAP vs. CPAP	WL+CPAP vs. WL	WL vs. CPAP
Body weight, Kg							
Modified ITT	**Change, Week 8**	0.3 (-1.2 to 1.7)	-3.0 (-4.6 to -1.4)	-4.4 (-5.9 to -2.8)			
Sample	**Change, Week 24**	0.7 (-1.1 to 2.5)	-7.1 (-8.9 to -5.3)	-6.9 (-8.8 to -5.1)	<0.0001	0.89	<0.0001
Adherent	**Change, Week 8**	0.1 (-1 to 1.1)	-5.6 (-7.0 to -4.2)	-6.3 (-7.6 to -5.1)			
Subjects	**Change, Week 24**	0.5 (-1.1 to 2.0)	-11.5 (-13.5 to -9.4)	-10.5 (-12.4 to -8.7)	<0.0001	0.50	<0.0001
Percent change in CRP							
Modified ITT	**Change, Week 8**	-8.81 (-23.22 to 8.32)	-15.98 (-29.7 to 0.43)	-15.25 (-29.09 to 1.3)	0.054	0.59	0.013
Sample	**Change, Week 24**	-7.24 (-21.4 to 9.46)	-26.73 (-38.38 to -12.88)	-31.4 (-42.2 to -18.58)			
Adherent	**Change, Week 8**	-6.4 (-21.86 to 12.12)	-20.02 (-37.22 to 1.91)	-16.91 (-33.66 to 4.08)	0.075	0.65	0.014
Subjects	**Change, Week 24**	-11.47 (-26.09 to 6.03)	-32.66 (-47.14 to -14.22)	-37.45 (-49.23 to -22.94)			
Insulin Sensitivity Index, ($\times 10^{-4}$/min^{-1} /µU/mL)							
Modified ITT	**Change, Week 8**	0.32 (0 to 0.65)	0.3 (-0.02 to 0.63)	0.19 (-0.16 to 0.54)			
Sample	**Change, Week 24**	0.05 (-0.27 to 0.36)	0.63 (0.31 to 0.95)	0.44 (0.11 to 0.77)	0.012	0.42	0.09
Adherent	**Change, Week 8**	0.4 (-0.01 to 0.81)	0.31 (-0.2 to 0.81)	0.08 (-0.43 to 0.58)			
Subjects	**Change, Week 24**	0.06 (-0.34 to 0.46)	0.74 (0.24 to 1.23)	0.43 (-0.04 to 0.9)	0.038	0.38	0.24
Triglycerides (mg/dL)							
Modified ITT	**Change, Week 8**	-10.7 (-22.7 to 1.4)	-25.8 (-38.9 to -12.7)	-7.31 (-20.1 to 5.5)			
Sample	**Change, Week 24**	-7.9 (-24.4 to 8.6)	-32.2 (-49.4 to -15.0)	-19.0 (-36.5 to -1.5)	0.046	0.29	0.36
Adherent	**Change, Week 8**	-4.7 (-18.0 to 8.5)	-35.2 (-53.3 to -17.2)	-12.9 (-29.3 to 3.4)			
Subjects	**Change, Week 24**	-7.1 (-24.2 to 10)	-53 (-76 to -30.2)	-23.2 (-43.8 to -2.6)	0.002	0.06	0.23
LDL-Cholesterol (mg/dL)							
Modified ITT	**Change, Week 8**	-6.24 (-11.89 to -0.59)	-4.39 (-10.54 to 1.76)	-10.48 (-16.5 to -4.47)			
Sample	**Change, Week 24**	-2.92 (-9.07 to 3.23)	-6.04 (-12.46 to 0.37)	-8.0 (-14.52 to -1.48)	0.49	0.67	0.26
Adherent	**Change, Week 8**	-6.65 (-12.4 to -0.9)	-12.8 (-20.63 to -4.96)	-12.45 (-19.51 to -5.4)			
Subjects	**Change, Week 24**	-3.76 (-10.08 to 2.55)	-13.54 (-22.03 to -5.05)	-9.25 (-16.87 to -1.6)	0.07	0.46	0.27
HDL-Cholesterol (mg/dL)							

		CPAP	WL+CPAP	WL	*Between-group P value, Week 24*		
					WL+CPAP vs. CPAP	**WL+CPAP vs. WL**	**WL vs. CPAP**
Systolic BP (mmHg)							
Modified ITT	**Change, Week 8**	-6.6 (-9.8 to -3.4)	-5.4 (-8.7 to -2.1)	-4.5 (-7.9 to -1.1)			
Sample	**Change, Week 24**	-4.2 (-7.7 to -0.6)	-7.8 (-11.4 to -4.3)	-5.1 (-8.7 to -1.4)	0.15	0.29	0.72
Adherent	**Change, Week 8**	-5.6 (-9 to -2.1)	-2.5 (-7.1 to 2.1)	-3.5 (-7.9 to 0.8)			
Subjects	**Change, Week 24**	-3 (-6.5 to 0.5)	-14.1 (-18.7 to -9.5)	-6.8 (-10.8 to -2.7)	0.0003	0.02	0.16
Mean Arterial Pressure (mmHg)							
Modified ITT	**Change, Week 8**	-4.9 (-7.4 to -2.4)	-5.9 (-8.4 to -3.4)	-4.8 (-7.4 to -2.1)			
Sample	**Change, Week 24**	-4.2 (-6.8 to -1.7)	-6.5 (-9.1 to -3.9)	-3.7 (-6.4 to -1)	0.21	0.13	0.78
Adherent	**Change, Week 8**	-3.8 (-6.4 to -1.2)	-3.4 (-6.8 to 0.03)	-4.2 (-7.4 to -1)			
Subjects	**Change, Week 24**	-3.5 (-6.1 to -0.9)	-10.6 (-14 to -7.2)	-4.7 (-7.7 to -1.7)	0.001	0.01	0.54
Pulse Pressure (mmHg)							
Modified ITT	**Change, Week 8**	-2.8 (-5.7 to 0.1)	-0.2 (-3.2 to 2.7)	0.56 (-2.5 to 3.6)			
Sample	**Change, Week 24**	0.2 (-2.6 to 3)	-3 (-5.8 to -0.1)	-2.3 (-5.1 to 0.6)	0.12	0.73	0.23
Adherent	**Change, Week 8**	-2.8 (-6.2 to 0.7)	0.2 (-4.4 to 4.8)	1.6 (-2.8 to 5.9)			
Subjects	**Change, Week 24**	1 (-1.7 to 3.7)	-6.2 (-9.8 to -2.7)	-3.4 (-6.6 to -0.3)	0.001	0.24	0.038
LDL-Particle Concentration (nmol/L)							
Modified ITT	**Change, Week 8**	-20.9(-89.2 to 47.5)	-86.4 (-156.1 to -16.6)	-92.6 (-165.8 to -19.4)			
Sample	**Change, Week 24**	-12.7 (-90.1 to 64.7)	-62.3 (-142.2 to 17.6)	-100.9 (-183.4 to -18.4)	0.38	0.51	0.13
Adherent	**Change, Week 8**	-46.0 (-116.3 to 24.3)	-117.99 (-211.2 to -24.8)	-147.3 (-237.0 to -57.5)			
Subjects	**Change, Week 24**	-39.5 (-129.7 to 50.8)	-33 (-151.8 to 85.9)	-177.3 (-285 to -69.7)	0.93	0.08	0.06
HDL-Particle Concentration (nmol/L)							
Modified ITT	**Change, Week 8**	-0.4 (-1.5 to 0.6)	-1.4 (-2.4 to -0.3)	-1.3 (-2.4 to -0.2)			
Sample	**Change, Week 24**	0.2 (-0.9 to 1.3)	-0.2 (-1.3 to 1)	-0.5 (-1.7 to 0.7)	0.62	0.68	0.36
Adherent	**Change, Week 8**	-0.4 (-1.6 to 0.8)	-1.6 (-3.2 to 0.02)	-2.0 (-3.5 to -0.4)			
Subjects	**Change, Week 24**	0.3 (-0.9 to 1.6)	-0.6 (-2.3 to 1.1)	-0.8 (-2.3 to 0.7)	0.37	0.86	0.25

CRP = C-reactive Protein; BP = blood pressure; LDL = low-density lipoprotein; HDL=high-density lipoprotein. ITT=Intention to treat.

Table S4. Change in Body Weight and Various Study Endpoints from baseline, at 8 weeks and 24 weeks, in sensitivity analyses that included all randomized subjects, using the baseline value carried forward for subjects who did not attend 8-week or 24-week follow-up study visits.

		CPAP	WL+CPAP	WL	*Between-group P value, Week 24*		
					WL+CPAP vs. CPAP	WL+CPAP vs. WL	WL vs. CPAP
Body weight, Kg	**Change, Week 8**	0.09 (-1.10 to 1.28)	-2.26 (-3.41 to -1.11)	-2.79 (-3.95 to -1.63)			
	Change, Week 24	0.49 (-1.07 to 2.04)	-5.02 (-6.52 to -3.52)	-4.90 (-6.41 to -3.39)	<0.0001	0.92	<0.0001
Percent change in CRP	**Change, Week 8**	-8.45 (-19.11 to 3.62)	-13.54 (-23.3 to -2.54)	-9.55 (-19.84 to 2.05)			
	Change, Week 24	-5.94 (-17.53 to 7.28)	-22.64 (-31.88 to -12.15)	-22.65 (-31.96 to -12.07)	0.036	0.99	0.037
Insulin Sensitivity Index, $\times 10^{-4}$/min^{-1} /μU/mL	**Change, Week 8**	0.22 (-0.007 to 0.45)	0.21 (-0.01 to 0.43)	0.13 (-0.09 to 0.35)			
	Change, Week 24	-0.02 (-0.23 to 0.20)	0.42 (0.21 to 0.63)	0.25 (0.04 to 0.46)	0.005	0.25	0.09
Triglycerides, mg/dL	**Change, Week 8**	-7.69 (-16.06 to 0.68)	-14.37 (-22.47 to -6.27)	-5.16 (-13.33 to 3.00)			
	Change, Week 24	-3.22 (-14.28 to 7.85)	-19.65 (-30.34 to -8.95)	-10.34 (-21.12 to 0.45)	0.037	0.23	0.36
LDL-Cholesterol, mg/dL	**Change, Week 8**	-4.34 (-8.37 to -0.31)	-3.02 (-6.92 to 0.87)	-6.31 (-10.24 to -2.38)			
	Change, Week 24	-2.66 (-6.73 to 1.42)	-2.62 (-6.56 to 1.32)	-4.64 (-8.61 to -0.67)	0.99	0.48	0.49
HDL-Cholesterol, mg/dL	**Change, Week 8**	-1.26 (-2.39 to -0.12)	-0.76 (-1.86 to 0.34)	-1.04 (-2.15 to 0.07)	0.44	0.73	0.26
	Change, Week 24	-0.64 (-1.81 to 0.53)	0.01 (-1.13 to 1.14)	0.30 (-0.85 to 1.44)			
Systolic BP, mmHg	**Change, Week 8**	-4.87 (-7.30 to -2.44)	-4.04 (-6.39 to -1.70)	-3.25 (-5.61 to -0.88)			
	Change, Week 24	-3.07 (-5.82 to -0.32)	-5.64 (-8.30 to -2.98)	-3.38 (-6.07 to -0.70)	0.19	0.24	0.87
Mean Arterial Pressure, mmHg	**Change, Week 8**	-3.70 (-5.62 to -1.77)	-4.25 (-6.11 to -2.39)	-3.20 (-5.08 to -1.32)			
	Change, Week 24	-3.15 (-5.16 to -1.14)	-4.60 (-6.55 to -2.66)	-2.49 (-4.44 to -0.53)	0.31	0.13	0.64
Pulse Pressure, mmHg	**Change, Week 8**	-1.96 (-4.04 to 0.12)	-0.52 (-2.53 to 1.50)	-0.07 (-2.10 to 1.95)			
	Change, Week 24	0.12 (-2.01 to 2.25)	-2.10 (-4.17 to -0.04)	-1.5 (-3.58 to 0.58)	0.14	0.68	0.28

CRP = C-reactive Protein; BP = blood pressure; LDL = low-density lipoprotein; HDL=high-density lipoprotein.

Table S5. Adverse Events Reported during the trial. Numbers represent the number of subjects with specific events

	CPAP-only	Weight Loss-Only	Combination therapy
Nasal Congestion	2	0	1
Upper respiratory infection	6	8	4
Flu	1	1	0
Irritation of Nostrils	1	0	4
Worsening of Respiratory Allergy Symptoms	0	0	1
Any of upper respiratory events listed above	10	9	10
"Shakiness" After IVGTT	0	0	2
Burning Sensation after IVGTT	1	0	0
Lump at site of IV	0	0	1
Bruising/Tenderness - IV	0	1	1
Vomited during IVGTT	0	1	0
Rash from Lead	0	0	1
Eye Irritation	0	0	3
High BP	0	1	1
Chest Pain	1	1	2
Headache	0	0	1
Bronchitis	0	1	0
Laryngitis	0	0	1
Type II Diabetes	0	0	2
Motor Vehicle Accident	0	0	2
Self Committed to Hospital	1	0	0
Depression	0	1	0
Tendonitis of Shoulder	0	1	0
Rash	0	1	0
Swelling in legs and ankles	1	0	0
Knee Replacement Surgery	1	0	0
Wisdom Teeth Removal	0	0	1
Rotator Cuff Surgery	0	1	0
Knee Pain	0	0	1
Leg Cramps	0	0	1
Panic Attack	0	1	0
Palpitations	0	0	1
Pain in ankle/lower back	0	1	0
Back Pain	0	1	0
Dehydration	1	0	0
Sprained Wrist/Bruised Knee	1	0	0
Right Flank Pain	0	0	1
Tooth Extraction and Implant	1	0	0
Possible urinary tract infection	0	0	1

New diagnosis of Fibromyalgia	0	0	1
Intestinal Cramping	0	0	1
Right Shoulder Pain	1	0	0
Ankle Injury	1	0	0
Abdominal Pain/Kidney Stone	0	0	1

IV = intravenous; FSIGTT = frequently-sampled intravenous glucose tolerance test.

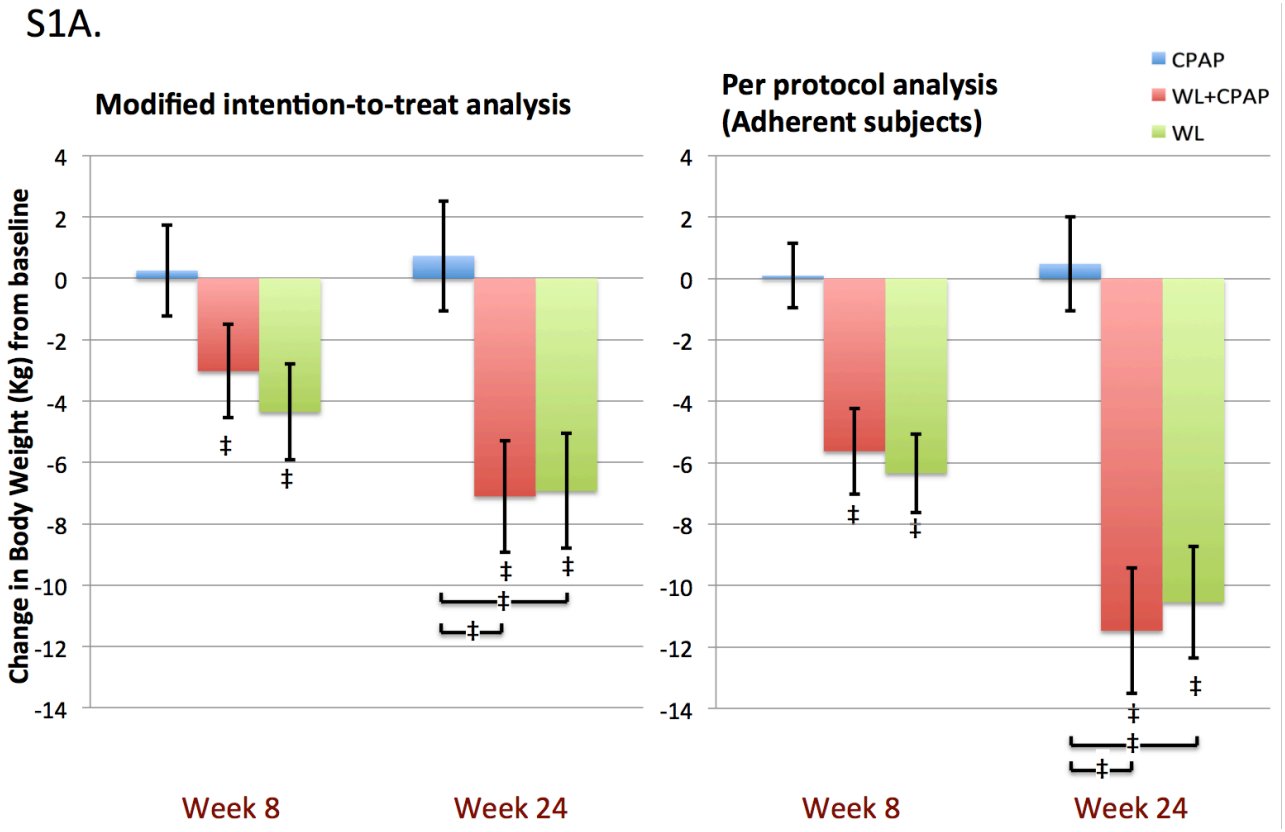
Table S6. Sensitivity analyses assessing the change in blood pressure from baseline, at 8 weeks and 24 weeks, among subjects who did not experience changes in antihypertensive medication use

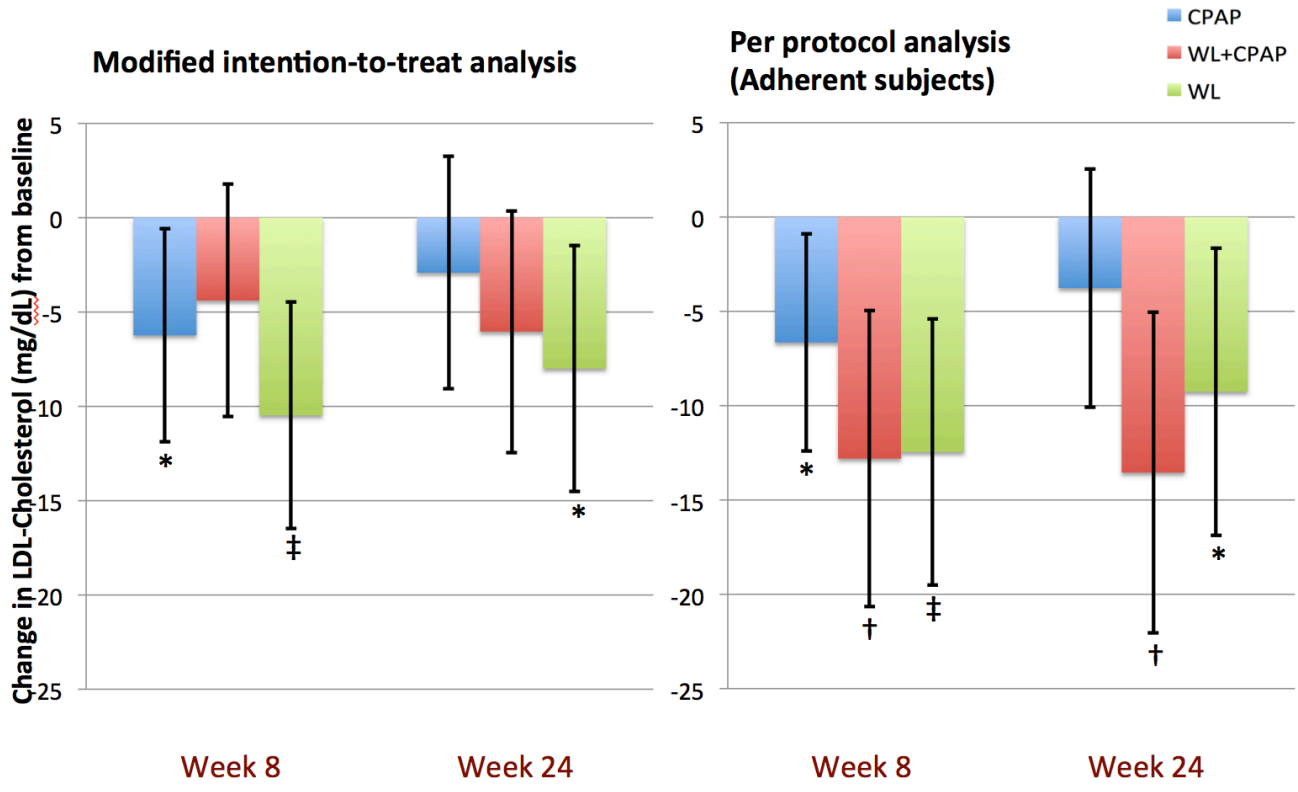
		CPAP	WL+CPAP	WL	*Between-group P value, Week 24*		
					WL+CPAP vs. CPAP	WL+CPAP vs. WL	WL vs. CPAP
Systolic BP (mmHg)							
Modified ITT	**Change, Week 8**	-5.6 (-9.0 to -2.2)	-5.0 (-8.3 to -1.7)	-5.0 (-8.5 to -1.5)			
Sample	**Change, Week 24**	-4.0 (-7.8 to -0.2)	-7.7 (-11.3 to -4.0)	-5.6 (-9.5 to -1.7)	0.17	0.44	0.56
Adherent	**Change, Week 8**	-4.8 (-8.4 to -1.1)	-2.5 (-7.0 to 2.0)	-4.6 (-9.0 to 0.1)			
Subjects	**Change, Week 24**	-2.7 (-6.3 to 1.0)	-14.1 (-18.6 to -9.6)	-7.9 (-12.2 to -3.7)	0.0002	0.052	0.064
Mean Arterial Pressure (mmHg)							
Modified ITT	**Change, Week 8**	-4.7 (-7.3 to -2.1)	-5.7 (-8.2 to -3.2)	-5.2 (-7.9 to -2.6)			
Sample	**Change, Week 24**	-4.6 (-7.3 to -1.8)	-6.4 (-9.1 to -3.8)	-4.1 (-6.9 to -1.3)	0.34	0.23	0.81
Adherent	**Change, Week 8**	-3.7 (-6.3 to -1.1)	-3.4 (-6.6 to -0.16)	-5.1 (-8.3 to -1.9)			
Subjects	**Change, Week 24**	-3.7 (-6.4 to -1.0)	-10.6 (-13.9 to -7.3)	-5.5 (-8.6 to -2.4)	0.002	0.029	0.40
Pulse Pressure (mmHg)							
Modified ITT	**Change, Week 8**	-1.6 (-4.6 to 1.4)	-0.02 (-2.9 to 2.9)	0.51 (-2.6 to 3.6)			
Sample	**Change, Week 24**	1.0 (-2.0 to 4)	-2.9 (-5.8 to -0.1)	-2.5 (-5.6 to 0.5)	0.07	0.86	0.11
Adherent	**Change, Week 8**	-1.6 (-5.2 to 2.1)	0.2 (-4.3 to 4.7)	1.4 (-3.0 to 5.9)			
Subjects	**Change, Week 24**	1.8 (-1.1 to 4.6)	-6.2 (-9.7 to -2.7)	-4.1 (-7.4 to -0.8)	0.0007	0.37	0.009

Figure S1. Changes in body weight (A), LDL-cholesterol (B), HDL-cholesterol (C), LDL-particle concentration (D) and HDL-particle concentration (E) compared to baseline in modified intention-to-treat analyses (left panels) and per-protocol analyses including only subjects who met pre-specified adherence criteria (right panels). Error bars represent 95% confidence intervals. Symbols above or below each column represent the statistical significance of the change from baseline within each group. No significant between-group differences in these changes were found. * $P<0.05$; † $P<0.01$; ‡ $P<0.001$.

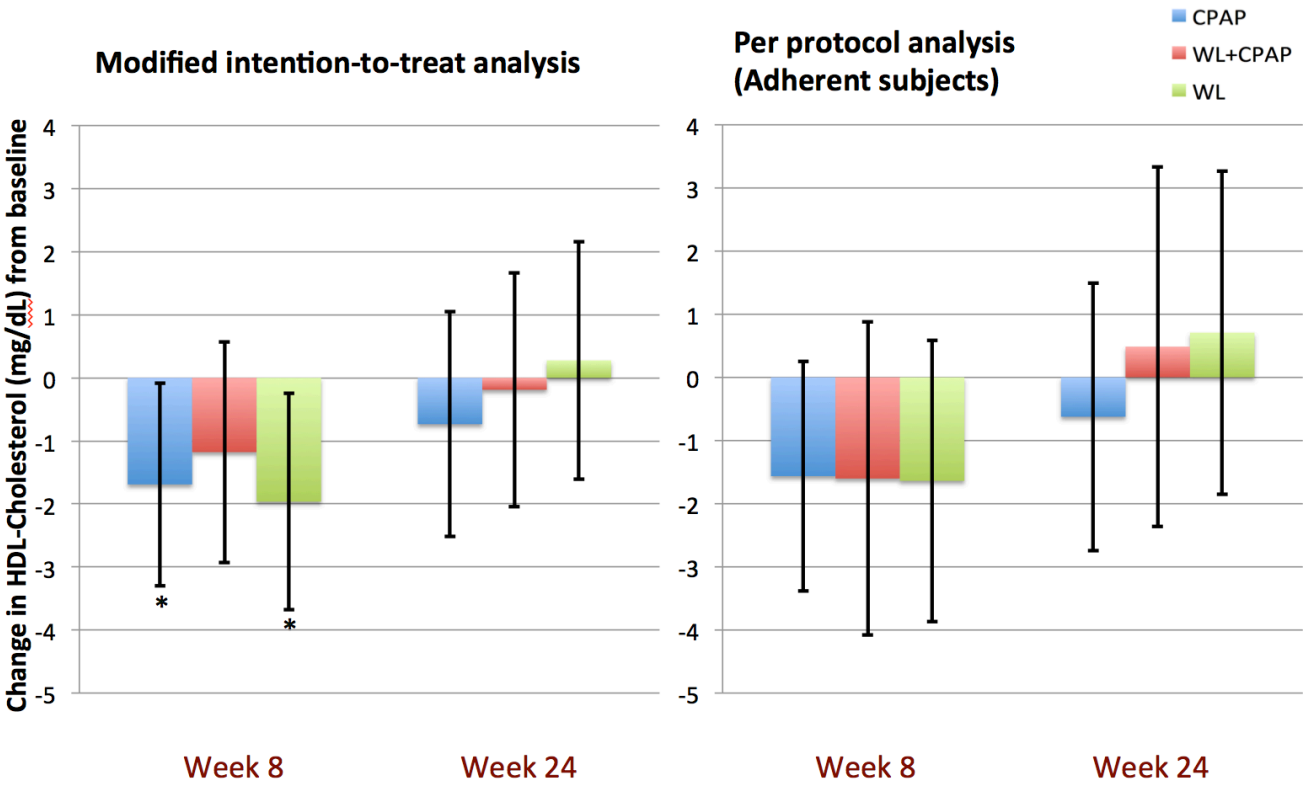
Figure S2. Changes in mean arterial pressure (A) and pulse pressure (B) compared to baseline in modified intention-to-treat analyses (left panels) and per-protocol analyses including only subjects who met pre-specified adherence criteria (right panels). Error bars represent 95% confidence intervals. Symbols above or below each column represent the statistical significance of the change from baseline within each group. No significant between-group differences in these changes were found. * $P<0.05$; † $P<0.01$; ‡ $P<0.001$.

Figure S1.

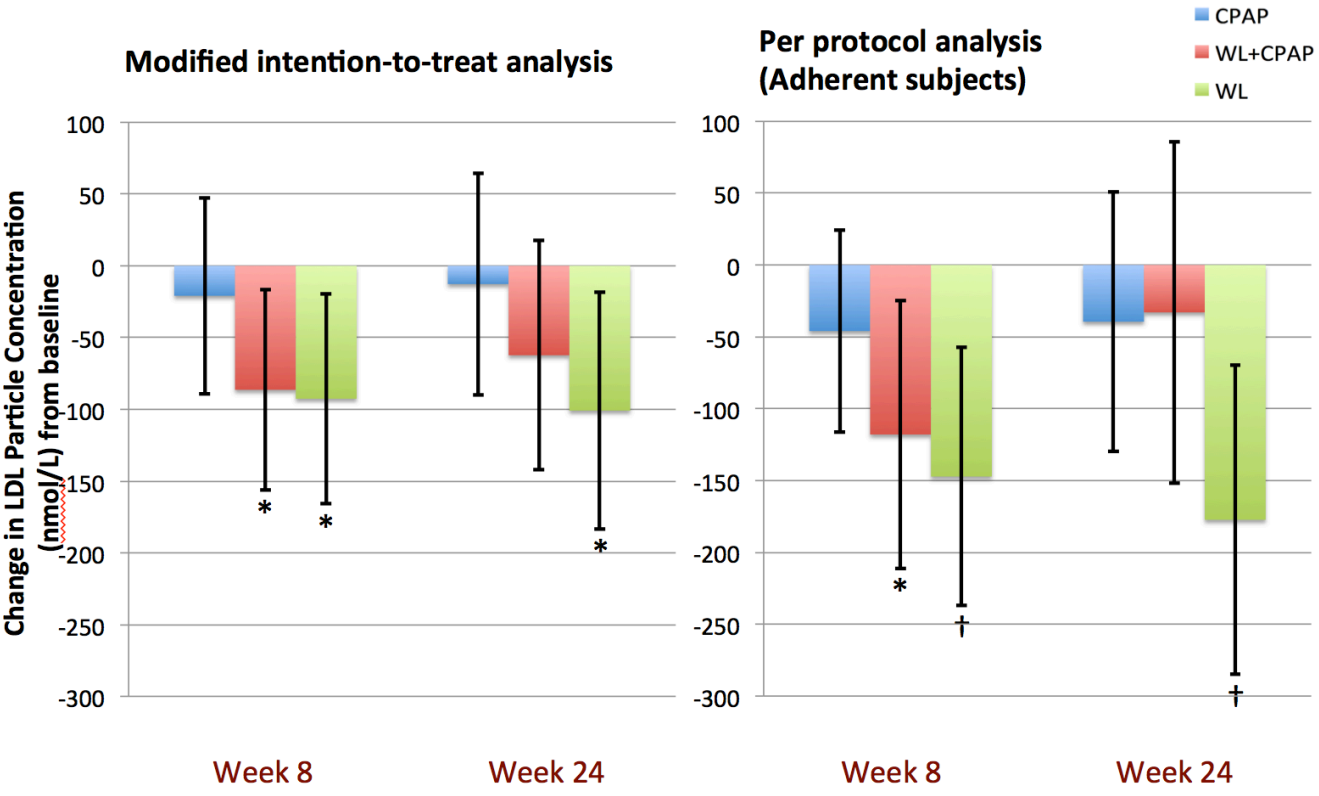

S1A.
Modified intention-to-treat analysis
Per protocol analysis
(Adherent subjects)
CPAP
WL+CPAP
WL
Change in Body Weight (Kg) from baseline
4
2
0
-2
-4
-6
-8
-10
-12
-14
‡
Week 8
Week 24
Week 8
Week 24


S1B.
Modified intention-to-treat analysis
Per protocol analysis
(Adherent subjects)
CPAP
WL+CPAP
WL
Change in LDL-Cholesterol (mg/dL) from baseline
5
0
-5
-10
-15
-20
-25
*
†
‡
Week 8
Week 24
Week 8
Week 24

S1C.


Modified intention-to-treat analysis
Per protocol analysis
(Adherent subjects)
CPAP
WL+CPAP
WL
Change in HDL-Cholesterol (mg/dL) from baseline
4
3
2
1
0
-1
-2
-3
-4
-5
*
*
Week 8
Week 24
Week 8
Week 24

S1D.


Modified intention-to-treat analysis
Per protocol analysis
(Adherent subjects)
CPAP
WL+CPAP
WL
Change in LDL Particle Concentration (nmol/L) from baseline
100
50
0
-50
-100
-150
-200
-250
-300
*
*
*
*
†
†
Week 8
Week 24
Week 8
Week 24

S1E.

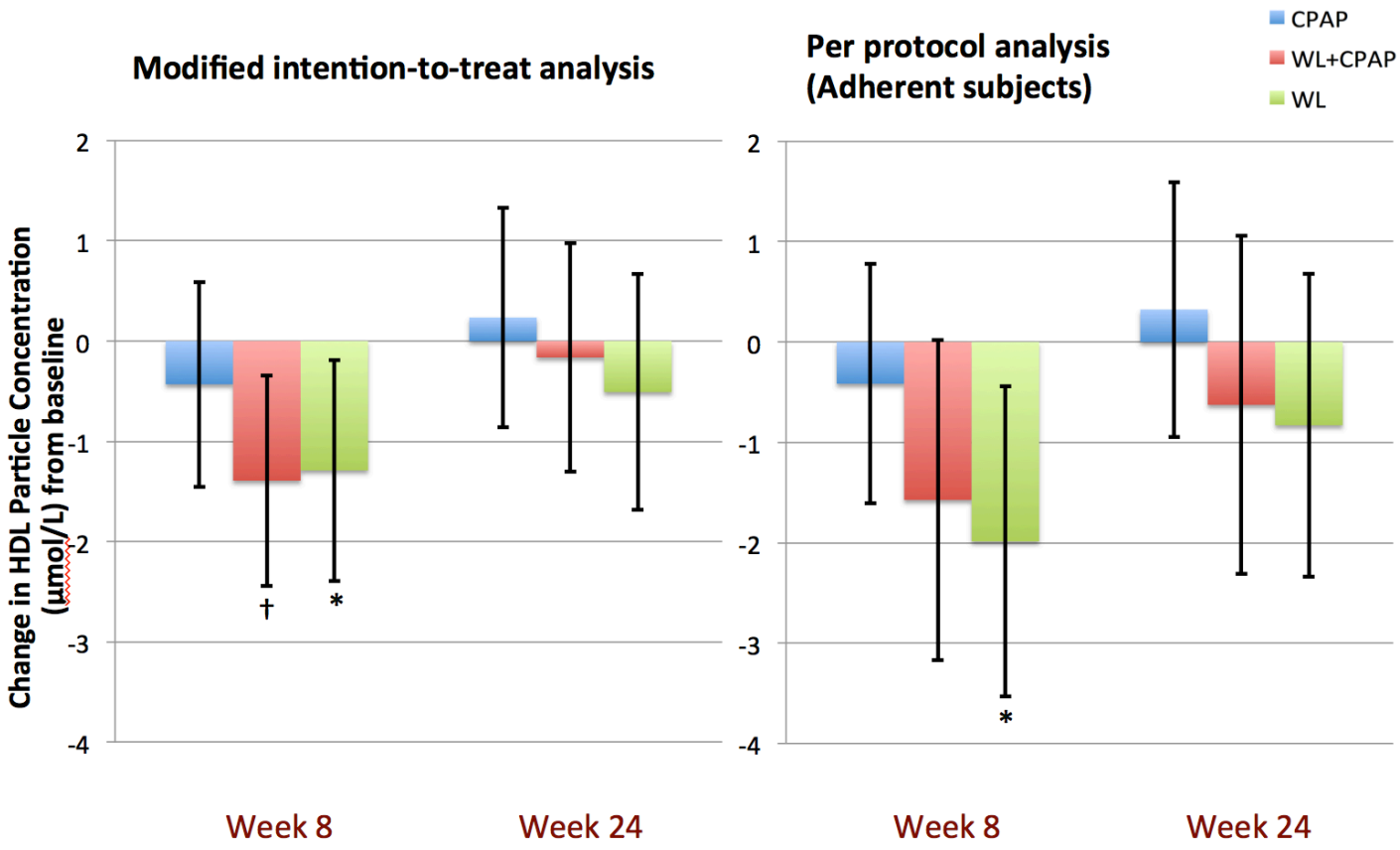
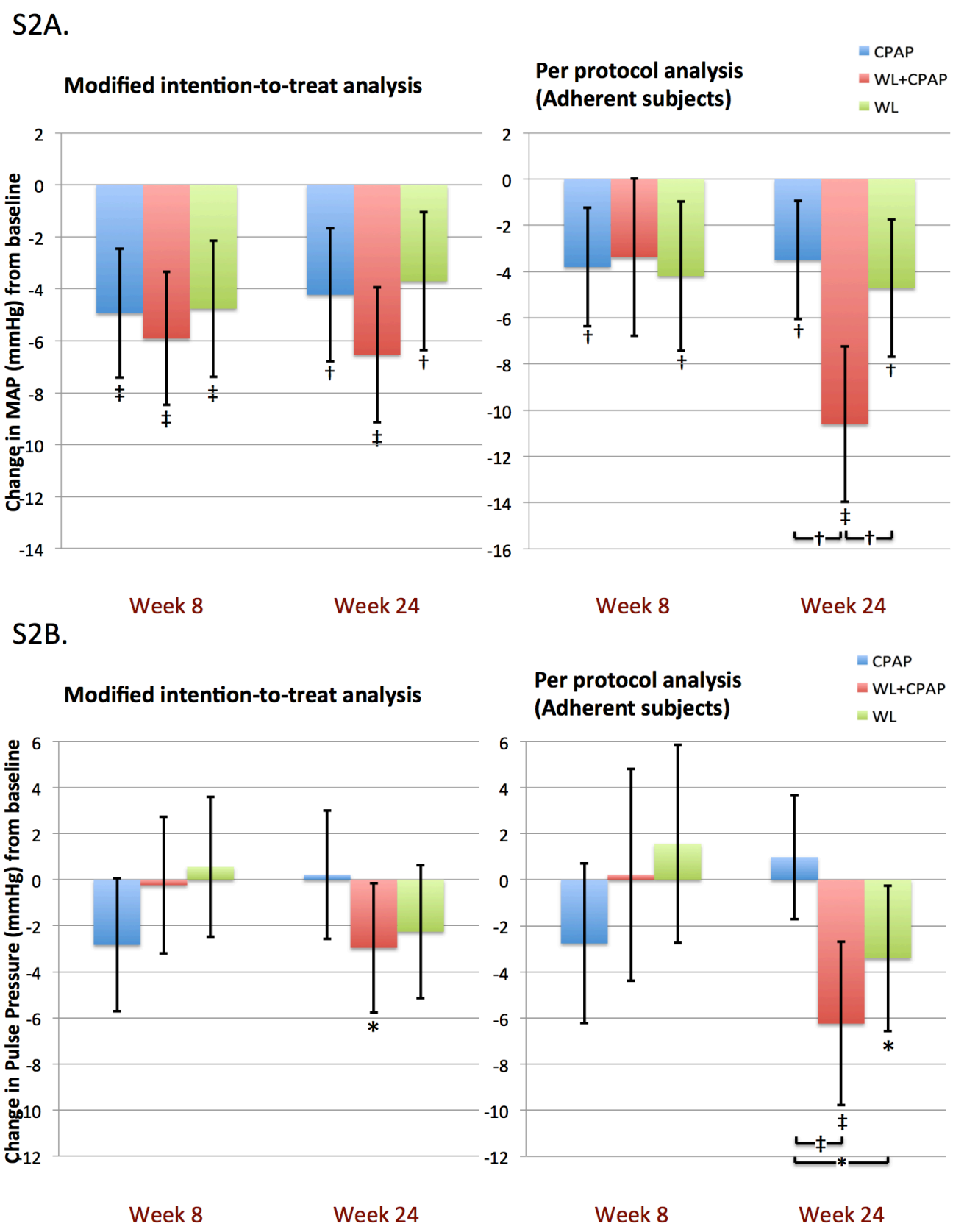

Modified intention-to-treat analysis
Per protocol analysis
(Adherent subjects)
CPAP
WL+CPAP
WL
Change in HDL Particle Concentration (µmol/L) from baseline
2
1
0
-1
-2
-3
-4
†
*
*
Week 8
Week 24
Week 8
Week 24

Figure S2.


S2A.
Modified intention-to-treat analysis
Per protocol analysis
(Adherent subjects)
CPAP
WL+CPAP
WL
Change in MAP (mmHg) from baseline
Week 8
Week 24
Week 8
Week 24
S2B.
Modified intention-to-treat analysis
Per protocol analysis
(Adherent subjects)
CPAP
WL+CPAP
WL
Change in Pulse Pressure (mmHg) from baseline
Week 8
Week 24
Week 8
Week 24

References

1. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992;15:173-84.
2. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5.
3. Bergman RN, Prager R, Volund A, Olefsky JM. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. J Clin Invest 1987;79:790-800.
4. Boston RC, Stefanovski D, Moate PJ, Sumner AE, Watanabe RM, Bergman RN. MINMOD Millennium: a computer program to calculate glucose effectiveness and insulin sensitivity from the frequently sampled intravenous glucose tolerance test. Diabetes Technol Ther 2003;5:1003-15.
5. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. Clinics in laboratory medicine 2006;26:847-70.
6. Sidhu JS, Cowan D, Kaski JC. The Effects of Rosiglitazone, a Peroxisome Proliferator-Activated Receptor-Gamma Agonist, on Markers of Endothelial Cell Activation, C-reactive Protein, and Fibrinogen Levels in Non-Diabetic Coronary Artery Disease Patients. J Am Coll Cardiol 2003;42:1757-63.
7. Pasceri V, Chang J, Willerson JT, Yeh ETH. Modulation of C-Reactive Protein-Mediated Monocyte Chemoattractant Protein-1 Induction in Human Endothelial Cells by Anti-Atherosclerosis Drugs. Circulation 2001;103:2531-4.
8. Ishibashi M, Egashira K, Hiasa K-I, et al. Antiinflammatory and Antiarteriosclerotic Effects of Pioglitazone. Hypertension 2002;40:687-93.
9. Wang TD, Chen WJ, Lin JW, Chen MF, Lee YT. Effects of Rosiglitazone on Endothelial Function, C-Reactive Protein, and Components of the Metabolic Syndrome in Nondiabetic Patients With the Metabolic Syndrome. Am J Cardiol 2003;93:362-5.